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EXAMINER	
VOGEL, NANCY S	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,116	BAKER ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-32 are pending in the case.

Receipt of the Information Disclosure Statement and Declarations of Dr. Polakis (II) and Dr. Scott is acknowledged.

Claim Rejections - 35 USC § 101 and 112 first paragraph

Claims 28-32 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 28-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

These rejection are maintained essentially for the reasons made of record in the previous Office action, mailed 8/21/06.

The claims are directed to antibodies that bind a polypeptide of SEQ ID NO:194, i.e. the PRO1303 polypeptide. The specification also discloses that PROI303 tested positive as stimulators of glucose and/or FFA (free fatty acid) uptake. The asserted utility based upon this assay result is that the polypeptide would be expected to be useful for the therapeutic treatment of disorders where either stimulation or uptake by adipocytes would be beneficial inhibition of glucose for example, obesity, diabetes, or hyper- or hypo-insulinemia. **First**, the specification does not indicate which asserted

utilities correspond specifically to glucose uptake stimulation as opposed to glucose uptake inhibition. **Second**, the specification does not indicate what, any of the utilities set forth correspond to stimulation of FFA uptake. **Third**, the actual assay result is stimulation of glucose and/or FFA uptake, three very different activities (stimulation of glucose uptake only, stimulation of FFA uptake only, and stimulation of uptake of both). Would PROI3O3 polypeptides be useful to treat hyper- insulinemia or would it be useful to treat hypo-insulinemia, two opposite conditions? **Fourth**, it is unclear how increasing uptake of FFA into adipocytes would treat obesity (or thus diabetes). Fabris et al teaches that in obesity, excessive energy storage as fat is mainly due to an imbalance between energy intake and expenditure, and the preferential channeling of excess calories as fat rather than protein or glycogen may play an important role in the development and maintenance of the disease. FFA-induced insulin resistance saves scarce glucose for central nervous system requirements, but this becomes counterproductive in obesity because it inhibits glucose utilization when there is no need to save glucose and FFA might thus be channeled toward tissues (such as adipose tissue in which insulin sensitivity is maintained or even improved) (page 601, second column). Thus, increase of uptake of FFA and/or glucose into adipocytes does not appear to be a utility for treatment of obesity or diabetes. Furthermore, the observed differences do not appear to be statistically significant and the cutoff points appear to be arbitrary and there is not obvious scientific basis for them. For example, Santomauro et al. (1999. Diabetes 48:1836-1841) teach that 56.5% decreases in FFA levels are statistically significant and correlated with physiological improvements, but it is not clear

from either the prior art or the specification whether 50% decreases are useful (see Table 2 from Santomauro et a1.). Note that 50% decreases in plasma insulin do appear to be significant, but is not clear whether this is due to a doubling of insulin uptake by adipocytes or by other tissues, or whether it is due to changes in the amount of insulin production. Similarly, the observation that 56.5% decreases in circulating FFAS is significant and correlated with physiological improvements does not indicate that a doubling of uptake of FFAS by adipocytes will lead to the same decreases in FFAS. For example, doubling the amount of FFA uptake from 1% to 2% of total circulating FFAS would not be expected to lead to a 56% decrease in circulating FFA levels. Finally, it is noted that the result of a single in vitro assay, even if it were disclosed in the specification to show that FFA uptake was enhanced by the presence of PRO1303 in the culture medium, does not provide the utility **in currently available form** of treating humans for any condition listed, i.e. obesity, diabetes, hypo- or hyper-insulinemia (page 511 of the specification). Problems such as toxicity, method of delivery to appropriate cell types, stability in the bloodstream, dosage, etc. which would affect the utility in effective treatment of complex conditions such as obesity and diabetes have not been solved, or even contemplated to be approached, by the disclosure. Bathing a cell culture of adipocytes with culture media containing some unknown concentration of the claimed polypeptide whose function is totally unknown overnight hardly rises to the level of a utility in vivo for the treatment of complex disease conditions in a human being. Rather it constitutes a preliminary, though perhaps interesting, result in a screening type assay which would invite further experimentation before being actually useful for

treatment of the conditions disclosed. 35 U.S.C. 101 specifically requires that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. Because the instant specification, as filed, fails to disclose a specific role of PRO1303 in glucose and/or FFA uptake in adipocytes, one would have reasons to conclude that the instant invention, drawn to an antibody that binds said PRO1303, also does not have a utility, and therefore the invention was not completed as filed, and, therefore, clearly lacks utility in currently available form.

Another utility asserted by the specification is based upon gene amplification data for the gene encoding the PRO1303 polypeptide in colon and lung tumor. The specification asserts that amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers. However, the art shows that amplification data for genomic DNA have no bearing on the utility of the encoded polypeptides. tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS In order for PR0269 polypeptides to be overexpressed in lung USA 95214717-14722), who disclose that: '1An analysis of WISP-3 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and

overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISPQ DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." See p. 14722, second paragraph of left column', pp. 14720-14721 , "Amplification and Aberrant Expression of WISPS in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Phl template" (see abstract). Even if increased mRNA levels could be established for PRO1303, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1 :304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 31 1-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than I-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene

expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that mRNA (transcript) levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than so-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al.. (1999, Mol. Cell. Biol. 19:17207 1730) conducted a similar study with over 150 polypeptides. They concluded that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady- state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly

delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column). The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a poor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Greenbaum et al. (2003, Genome Biology 4:117.1-1 17.8) cautions against assuming that mRNA levels are generally correlative of protein levels The reference teaches (page 1 17.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into

protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their in vivo half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 1 17.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Therefore, data pertaining to PR01303 genomic DNA do not indicate anything significant regarding the claimed PR01303 polypeptides. The data do not support the specification's assertion that PR01303 polypeptides can be used as a cancer diagnostic agent or as a therapeutic drug development target. Significant further research would have been required of the skilled artisan to reasonably confirm that PR01303 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PR01303 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the antibodies that bind to PR01303 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the antibodies polypeptide. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by

> the public from an invention with substantial utility", "unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "(i)t is not a reward for the search, but compensation for its successful conclusion."

Applicant's arguments filed 11/28/06 have been considered but have not been found convincing.

Regarding applicant's arguments concerning the FFA assay results for PRO1303, applicant has presented a number of arguments stating that the result obtained for PRO1303 is sufficient to show a utility, and also to provide enablement for the use of PRO1303. However, it is maintained that the result is preliminary and at best invites further research in order to determine a substantial utility. As has been previously argued, the specification states that the PRO1303 tested positive as stimulator of "glucose and/or FFA uptake". While applicants argue that one of skill in the art would know which disorders would be treated with an agent which increases glucose uptake and FFA uptake. However, applicants statement that Santomauro demonstrated that "lowering of elevated plasma FFA levels can reduce insulin resistance/hyperinsulinema and improve oral glucose tolerance in lean and obese nondiabetic subjects and in obese patients with type 2 diabetes" does not indicate what the effect of increasing both glucose and FFA uptake, or increasing glucose or FFA uptake individually. Applicants present further arguments concerning prior art results for individual agents which have been the subject of study by other groups (pages 6-11).

However, the fact that other groups have studies other agents, and shown that they are effective in treating a particular disease state, does not indicate that the current PRO1303 has such a utility. The very preliminary result, of unclear significance, for PRO1303, for reasons of record, is not sufficient to show a substantial utility. Furthermore, they are not sufficient to show utility for antibodies which bind to the PRO1303.

Regarding the argument that the claimed antibodies are useful due to a positive result for the DNA encoding the PRO1303 in a gene amplification assay, it is maintained for reasons of record that there has not been shown a utility since there is no evidence that the protein is overexpressed. In response to the Examiner's arguments, at p. 13-15, Applicants take issue with the Pennica et al. and Konopka et al. references relied upon by the examiner. Specifically, Applicants characterize Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Applicants point out that there was such a correlation for WISP-1 as disclosed by Pennica et al. Applicants characterize Konopka et al. as being limited to the abl gene, and not speaking to genes in general. Applicants conclude that the examiner must show evidence that it is more likely than not that the correlation does not exist, and that a prima facie case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general because they show a lack of correlation between gene

amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in the majority of cases (Haynes et, Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al.), and (3) no evidence has been brought forth regarding levels of PRO1303 mRNA levels or PRO1303 polypeptide levels in cancerous tissue.

At p. 19-20 applicants argue that Haynes et al. support applicants' position when they state that there was a general trend between protein expression and transcript levels. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general.

At pp. 17-19, applicants criticize the Hu et al. reference. Specifically, Applicants criticize Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Applicants characterize Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Applicants criticize the types of statistical tests performed by Hu et al. Applicants conclude that, based on

the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to persuasive. The asserted utility for the claimed antibodies that bind PRO1303 polypeptide is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins (or their antibodies) as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO1303 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1303 protein or antibodies that bind it can be used as a cancer diagnostic. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression,

and thus the level of polypeptide expression must be tested empirically. Also, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas (the same type of cancer for which PRO1303 tested positive). Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO1303 mRNA or polypeptide is overexpressed in cancer, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Applicants' criticism of Hu et al.'s statistical analysis, Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide any statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicants' criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the

evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

At p. 23-25, Applicants argue that the Lian et al. publication is limited to differentiating myeloid cells and does not teach anything regarding a lack of correlation between mRNA levels and protein levels in general. Applicants also find fault with Lian et al. for using a relatively insensitive assay. This has been fully considered but is not found to be persuasive. Lian et al. show a lack of correlation between mRNA levels and polypeptide levels in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels.") This is directly on point for the instant issue. Furthermore, Applicants again hold the reference to a higher standard than their own specification. Lian et al. used an art-accepted method to measure polypeptide levels whereas the instant specification and evidence of record do not report using any method to detect PRO1303 polypeptide levels.

At p. 25-27, Applicants take issue with the Fessler et al. publication, stating that Fessler et al. is limited to studying a few proteins/RNAs and using an insensitive assay. This has been fully considered but is not found to be persuasive because Fessler et al. found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract), which is directly on point regarding the instant issue. Furthermore, Applicants again hold the reference to a higher standard than their own specification. Fessler et al. used an art-accepted method to measure

polypeptide levels whereas the instant specification and evidence of record do not report using any method to detect PRO1303 polypeptide levels.

At p. 15 , Applicants argue that Fessler et al. and Chen et al. are deficient for using 2D gels, which do not detect low abundance proteins. This has been fully considered but is not found to be persuasive. While 2D gels might exclude low abundance proteins, their use is valid for detectable proteins. Chen et al. focused on those mRNA which encoded proteins that were detectable on 2D gel (p. 308, col. 2). The method was sensitive enough to determine that proteins having different isoforms also often had different protein/mRNA correlation coefficients (p. 309, paragraph bridging col. 1-2). It was concluded that absolute protein level did not influence the correlation with mRNA (p. 310,col. 1). Additionally, the correlation coefficient was not arbitrarily chosen, but was based on detailed statistical analysis that resulted in those values above the assigned correlation coefficient to be considered significant if the designated difference was above the threshold (see paragraph bridging pages 307-308). The results of Chen lead to the conclusion that post-translation modifications are likely to affect the correspondence (or lack thereof) of mRNA to protein levels (see Discussion). Further it was shown (p. 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but

also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in levels of expression with their encoded proteins. 2D-PAGE is a common method of protein analysis, when the limitations are taken into account, as with Chen et al., the results are noteworthy.

Applicants argue that of the 66 genes with no isoforms, 40/66 had a positive correlation between mRNA and protein expression (Table 1). In Table II, which showed 30 genes with multiple isoforms, 22/30 showed a positive correlation between one isoform of each gene. No genes showed a negative isoform correlation. The argument has been fully considered, but is not persuasive. On page 309, first full sentence, Chen et al. state, "Among the 69 genes for which only a single protein spot was known (Table I), nine genes (9/69, 13%) were observed to show a statistically significant relationship between protein and mRNA abundance..." Table I considered significance at $p<0.05$. It is unclear what Applicants are using as the criteria for positive correlation to determine that 40/66 genes showed a correlation. If the correlation is not significant, one cannot support presumptions concerning it. As to Table II, if one isoform out of, for example, three shows a correlation, that finding supports the unpredictability of mRNA/protein correlation levels. Contrary to Applicants' assertion that no genes showed a negative isoform correlation, Q-1-Antitrypsin and PDI were shown to have such a negative isoform correlation. Further, a number of other proteins with isoform had some positive but insignificant correlations. Chen et al. is relied upon for teaching that assumptions cannot be made concerning mRNA/protein correlation with a reasonably certainty. The paper clearly answered the question posed: Does mRNA

expression correlate with protein expression in lung tumor samples? The answer was 'no' in a majority of cases. This result directly supports the Examiner's finding that the art does not sustain a reasonable expectation that for any particular mRNA expressed in tumor, the amount of protein and encoding mRNA will correlate.

Applicants argue that Hu et al., Lian et al., and Fessler et al. do not conclusively teach that, in general, protein levels cannot be accurately predicted from mRNA/gene amplification levels. Applicants argue that insensitive protein detection methods and methodology may have resulted in underrepresentation of certain protein species. Applicants urges that Haynes et al. and Chen et al. show a general positive correlation between increased gene amplification, mRNA and protein levels. Applicants conclude that a prima facie case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. In the instant case, the asserted utility that PRO1303 polypeptides and antibodies are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for a PRO1303 polypeptide or its antibodies to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO1303 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in healthy or diseased tissue (Haynes et al., Gygi et al., Lian et al., Fessler et al.,

Hu et al., LaBaer, Chen et al., Hanna et al.), and (3) no evidence has been brought forth regarding the levels of PRO1303 polypeptides in cancerous tissues.

In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO1303 polypeptides or their antibodies can be used as a cancer diagnostic agent.

At page 28 Applicants argue that Example 170 states that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer it is more likely than not that the encoded protein is overexpressed. Applicants point to Orntoft et al., Hyman et al., and Pollack et al. in support thereof. However, in response, it is maintained that Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused abundant proteins." (See abstract.) It would appear that Applicants have provided no fact or evidence concerning a correlation between the specification's disclosure of low levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene

amplification. This proportion approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1303 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At p.29, Applicants refer to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 . Applicants argue that this declaration provides the facts, set forth in a table (Exhibit B) for independent evaluation by the Examiner. The second Polakis declaration under 37 CFR 1.132 is insufficient to overcome the rejection for the following reasons. Specifically data for PRO 1303 does not appear in the table. Furthermore, it is not clear how the clones appearing in the table compare to PRO1303, or if the results presented in the table were determined by the same methodology as presented in the instant specification. For example, were the genes corresponding to the mRNAs tested amplified? How highly elevated were the mRNAs in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? By what means was the level of mRNA expression determined, e.g. microarray, Northern blot, quantitative PCR? The declaration only state that levels of mRNA and protein in tumor tissue were compared to normal tissue.

At [age 30, Applicants refer to the declaration of Dr. Scott, submitted under 37 C.F.R. § 1.132 . The Scott declaration under 37 CFR 1.132 is insufficient to overcome

the rejection for the following reasons. Applicant argues that Dr. Scott, an eminent researcher in this field, is of the opinion that mRNA levels correlate with protein levels.. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, (1)the nature of the fact sought to be established is whether or not mRNA levels are predictive of polypeptide levels in a sample. (2) The opposing evidence, cited by the examiner, is considerably strong. Please see the numerous references cited above, including Chen et al. and Greenbaum et al. (3) Dr. Scott does not appear to have an interest in the outcome of the case. (4) Finally, the Dr. Scott does not base his opinion an any particular facts other than his own considerable experience in the field. Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). While the declaration constitutes evidence that must be considered, there is also other evidence that mRNA levels are not predictive of polypeptide levels. The mere volume of contradictory publications on this topic speaks to the unpredictability of the issue.. Thus, consideration of the preponderance of the totality of the evidence indicates that the rejections should be maintained.

Applicants have submitted teachings from Alberts, B. (Molecular Biolo.qy of the Cell (3rd ed 1994 and 4med 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis I and Polakis II declarations). Applicants also cite numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc.). Applicants assert that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicants also contend that the references and the Polakis declarations establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. Applicants' arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is a common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3r~ ed., bottom of pg 453). Meric et al. states the following:

> "The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying

differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Celis et al. (200, FEBS Lett. 480:2-16) also teach that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (p. 6, col. 2). furthermore, with the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes et al. (80 proteins examined) and Chen et al. (165 proteins examined) (cited previously by Examiner) and Nagaraja et al. (2006, Oncogene 25:2328-2338), Waghray et al. (2001,

Proteomics 1:1327-1338) and Sagynaliev et al. (2005, Proteomics 5:3066-3078) (described below).

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one. Applicants' arguments with respect to Orntoft have been fully considered but are not found to 15e persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1303 in the instant specification. That is, it is not clear whether or not PRO1303 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear.

Applicants also assert that Futcher et al. (1999) conducted a study of mRNA and protein expression in yeast and report a good correlation between protein abundance, mRNA abundance, and codon bias. Applicants' arguments have been fully considered but have not been found persuasive. Futcher et al conclude that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis

added]" (p. 7368, col. 1). Futcher et al. also admit that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion. Futcher et al. indicate that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (p. 7367, col. 1, 1st full paragraph).

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies where significantly large numbers of transcripts and proteins were examined report that increases in mRNA and protein samples are not correlated. Nagaraja et al. (2006, Oncogene, 25:2328-2338) characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231) and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented the microarray designated profiles and vice versa" (see p. 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see p. 2328, second column). Lastly, Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see p. 2335, first column).

Similar results were reported by Waghray et al. (2001, Proteomics, 1:1327-338). Waghray et al. analyzed gene expression changes induced by ihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see p. 1333-1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (2005, Proteomics, 5:3066-3078) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see p. 3068). In summary, it is clear that Nagaraja et al., Waghray et al. and Sagynaliev et al. support the Examiner's position that changes in mRNA expression frequently do not result in changes in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO1303. There are no teachings in the specification as to the differential expression of PRO1303 mRNA in the

progression of lung cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicants' measurement of an increase of PRO1303 genomic DNA does not provide a specific and substantial utility for the encoded protein.

The state of the art, as evidenced through textbooks and review papers, clearly establishes that polypeptide levels cannot be accurately predicted from mRNA levels. Lilley et al. (2003, "Proteomics" Molecular Biology in Cellular Pathology, England: John Wiley & Sons, p. 351) teach that "DNA chips (mRNA profiling studies) can contribute to the study of gene expression in response to a particular biological perturbation. However, the extrapolation that changes in transcript level will also result in corresponding changes in protein amount or activity cannot always be made." Wildsmith et al. also disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pp. 269-286, especially p. 283). King et al. (2001, J. American Medical Assoc. 286:2280-2288) disclose that "it has been established that mRNA levels do not necessarily correlate with protein levels" (p. 2287, 2nd full paragraph). King et al. state that it has been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (p. 2287, bottom of col. 1 through the top of col. 2; see also Bork et al., 2000, Genome Res. 398-400, especially p. 398, bottom of col. 3). Haynes et al. teach that "[p]rotein expression levels are not predictable from the mRNA expression levels" (p.

1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Madoz-Gurpide et al. (2003, Adv. Exp. Med. Biol. 532:51-58) disclose that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels" (p. 53, Ist full paragraph). However, the specification of the instant application has only disclosed that the PRO1303 genomic DNA is amplified in some lung and colon tumor tissue samples. The specification suggests but does not show that the PRO1303 mRNA or polypeptide has been overexpressed in the lung and colon tumor samples tested. Given the asserted increase in PRO1303 expression, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the reported increase in PRO1303 genomic DNA supports a role for the encoded polypeptide in the cancerous tissue; such a role has not been established by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicants' claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and

> until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and, "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO1303 polypeptides, and the antibodies that bind them, have utility in the fields of cancer diagnostics is not substantial. Thus, consideration of the preponderance of the totality of the evidence indicates that the rejection under 35 U.S.C. § 101 and 112 first paragraph should be maintained.

Claims 28-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Ni et al., US Patent 6,566,498.

This rejection is maintained essentially for the reasons made of record in the previous Office action, mailed 8/28/06.

Ni et al teach an isolated human secreted polypeptide consisting of SEQ ID NO:6, which has two regions of 100% identity with a polypeptide consisting of SEQ ID NO:194, one 62 amino acids long (the first 62 amino acids) and one about 93 amino acids long (at the C-terminus). These large stretches of perfect identity between the two proteins only at each terminus of the proteins would appear to indicate that the two proteins are likely splice-variants of each other and thus re very likely to have

many exterior-exposed epitope domains in common. See the attached sequence comparison. Also, because antigenic epitopes can be as low as 7amino acids and preferably between 15 and 30 amino acids (Column 20 of Ni et al), any of the antibodies taught by the reference which are directed against the protein of SEQ ID NO:6 would strongly cross-react with and specifically bind to the polypeptide f SEQ ID N0:194. "Specifically binds" is interpreted in the claims as broad as is reasonable in the art, which encompasses antibody binding to a protein with a high affinity, of a level comparable with proteins having the identical epitope. The many stretches of 15 to 30 amino acids in common shows that many epitopes that would generate antibodies that specifically bind are in common between the two proteins. monoclonal and polyclonal antibodies are taught, as are antibody fragments, labeled antibodies, and humanized antibodies (columns 20-21 and 26).

Applicants argue that the antibodies of Ni et al. would not be considered to be antibodies that "specifically bind", since such an antibody must be able to bind to a specific epitope of the PRO1303 polypeptide without cross reacting with another epitope, including those found in the sequence disclosed in Ni et al. However, such a definition of "specifically bind" would not have been generally recognized in the art, and is not so defined in the specification. One would consider an antibody which specifically binds to any particular protein as one which recognizes a particular epitope. If the epitope is present in another protein and is recognized by the antibody, this would not cause one to conclude that the antibody does not "specifically bind" said protein. Therefore, applicants' arguments are not found convincing.

Conclusion

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 11/28/06 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant is advised that the instant Office action was made final because the same claims were maintained as rejected on the same grounds that have been of record. However, new references have been cited as evidence supporting the rejections of record, in response to the 151 new references cited by applicant. Applicant may submit counter-evidence in response to this office action, which will be appropriately entered after final. Alternatively, Applicant may wish to submit an Appeal Brief in response to this office action. Any inquiry concerning this communication or

earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 6:30 - 3:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NANCY VOGEL
PRIMARY EXAMINER

NV
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